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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,589	06/08/2000	Katherine A. High	018743/0276324	1864

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/589,589	HIGH ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/22/03*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,12-25,28-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,12-25,28-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/14/03 has been entered.

Claims 1-8, 10, 12-25, and 28-39 are pending examination.

The applicants' traversal, the amendment to claims 1, 3, 4, 10, 13, 14, 15, 16, 22, 24, and 25, the cancellation of claims 9, 11, 26, and 27, and the addition of claims 30-39 filed on 10/22/03 is acknowledged and considered.

Election/Restrictions

The election of species for claim 11 is moot because claim 11 was cancelled in the amendment filed on 10/22/03.

However, the non-elected species in amended claims 16 and 19, and new claims 32 and 37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

Claim Objections

Applicants are advised that should claim 3 be found allowable, claim 5 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The limitation "an increase in Factor IX is observed in said mammal," in claim 3 is inherent in claim 5 because the limitation is inherent in claim 1 (claim 3 and 5 depend from claim 1) because delivering Factor IX by way of gene therapy to a mammal would result in an increase in Factor IX observed in the said mammal.

Applicants are advised that should claim 12 be found allowable, claim 14 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicants are advised that should claim 20 be found allowable, claim 22 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicants are advised that should claim 23 be found allowable, claim 25 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 6, 17, and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how delivering a nucleic acid to a mammal results in delivering a blood coagulation protein.

Claims 17 and 18 are indefinite because the claims depend on each other and the examiner cannot determine what are the metes and bounds of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 3, 4, 5, 6, 10, 12, 13, 14, 15, 16, 19, 20, 22, 28, 29, 30, 31, 32, 33, 35, 37, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al. (US

6,251,957) taken with Bach (WO 96/25177) in further view of Tripathy et al., (Nat. Med. 1996, 2:545-550).

Wilson teaches a gene therapy method comprising co-administering with a viral vector an immunosuppressive agent to a human (column 2, lines 35-52, column 4, lines 20-34 and column 25-26). Wilson teaches co-administering cyclophosphamide (column 5, line 52-column 6, line 23 and column 8, lines 34-45). Wilson teaches that the immunosuppressive agent may be administered prior to or concurrently with the recombinant viral vector (column 2, lines 45-49). Wilson teaches that an immune response can be the product of the transgene when that transgene expresses a protein that is foreign to the treated host (column 1, lines 63-65). However, Wilson does not specifically teach using a viral vector comprising a nucleotide sequence encoding a blood coagulation protein and an immunosuppressive agent in a method of gene therapy.

However, at the time the invention was made, Bach teaches a method of combining an immunosuppressive agent and at least one adenovirus comprising a DNA containing a therapeutic gene (see abstract and page 3 of the US 2003/0004091, which is the English equivalent of WO 96/25177). Bach teaches that the invention makes it possible to achieve therapeutic effect, which is markedly prolonged (page 2 of the US 2003/0004091, which is the English equivalent of WO 96/25177). The DNA or therapeutic gene is from human (page 3 of the US 2003/0004091, which is the English equivalent of WO 96/25177). Bach teaches that the therapeutic gene can encode factors VII, VIII, and IX (page 3 of the US 2003/0004091, which is the English equivalent of WO 96/25177).

In addition, at the time the invention was made, Tripathy teaches that novel proteins delivered by way of gene therapy, including deficient human proteins in patients with recessive diseases generate immune responses (page 549).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson taken with Bach in further view of Tripathy to co-administer cyclophosphamide with a recombinant virus comprising a nucleotide sequence encoding a blood coagulation protein, e.g., Factor IX. One of ordinary skill in the art would have been motivated to combine the teaching because either Wilson or Bach teach that it is advantageous (prolonging therapeutic effect) to co-administer an immunosuppressive agent (e.g., cyclophosphamide) with a recombinant virus comprising a therapeutic gene. In addition, one of ordinary skill in the art would have been motivated to co-administer an immunosuppressive regimen with gene therapy because Tripathy, Wilson, and Bach teach that exposure of a novel human protein by way of gene therapy to a human deficient for the protein results in an immune response against the protein. Furthermore, the method taught by Wilson taken with Bach in further view of Tripathy has the same limitations as the claimed method. The method taught by Wilson taken with Bach in further view of Tripathy uses the same material(s) and method(s). Therefore, absence evidence to the contrary, one of ordinary skill in the art would reasonably conclude that the method would result in preventing or inhibiting the formation of inhibitory antibodies to a blood coagulation protein delivered to a mammal by way of gene therapy.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's argue that the prior art (High et al.,) does not describe that formation of inhibitory antibodies against a protein delivered via gene therapy can be prevented by administering an immunosuppressive agent.

Applicant's arguments filed 10/22/03 have been fully considered but they are not persuasive because High is not cited in the 103(a) rejection.

Furthermore, with respect to preventing the formation of inhibitory antibodies against a protein (Factor IX) delivered via gene therapy, Herzog et al., (Blood 1997, Vol. 90, No. 10, Part 1, Suppl [1], pp. 1057-1057) teaches the absence of antibodies against Factor IX following IM injection of an AAV vector encoding a species-specific transgene. Herzog further teaches that, "IM injection of an AAV vector expressing a species-specific transgene is not associated with antibody formation and that this approach is feasible for human gene therapy of hemophilia B."

Claims 1, 12, 13, 14, 23, 24, 25, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al. (US 6,251,957) taken with Bach (WO 96/25177) and Tripathy et al., (Nat. Med. 1996, 2:545-550) in further view of Nilsson (PNAS, 83:9169-9173, 1986) and Warrier (Blood Coagul Fibrinolysis, 1998 Mar;9 Suppl 1: S125-8).

The rejection of the base claims 1, 12, 13, and 14 under 35 U.S.C. 103(a) is applied here as indicated above, by Wilson taken with Bach in further view of Tripathy. However, Wilson taken with Bach and Tripathy do not specifically teach using the claimed method, wherein said mammal has no detectable endogenous expression of the blood coagulation protein or said human has hemophilia B and said inhibitory antibodies bind specifically with Factor IX protein.

However, at the time the invention was made, Nilsson teaches a complication of Factor IX therapy is the development of antibodies to Factor IX (page 9169).

Furthermore, at the time the invention was made, Warrier teaches that the development of inhibitory antibodies is a serious complication of hemophilia in young children. Inhibitors are commonly associated with the total absence of FIX antigen due to total deletions or other major derangements of the FIX gene.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson taken with Bach and Tripathy in further view of Nilsson and Warrier to co-administer an immunosuppressive agent with a viral vector comprising a nucleotide sequence encoding a FIX protein. One of ordinary skill in the art would have been motivated to combine the teaching because Nilsson and Warrier teach that the major problem with Factor IX therapy is the development of antibodies to Factor IX. In addition, Bach and Wilson teach using combination therapy to solve the problem with the immune response to a transgene that is foreign to the treated host.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 10/22/03 have been fully considered but they are not persuasive for the same reasons as set forth above in the prior 103(a) rejection.

Claims 1, 6, 7, 8, 12, 14, 33, 34, 35, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al. (US 6,251,957) taken with Bach (WO 96/25177) and Tripathy et

al., (Nat. Med. 1996, 2:545-550) in further view of Herzog et al., (IDS, PNAS, vol. 94, pages 5804-5809, 1997).

The rejection of the base claims 1, 12, and 14 under 35 U.S.C. 103(a) is applied here as indicated above, by Wilson taken with Bach in further view of Tripathy. However, Wilson taken with Bach and Tripathy do not specifically teach using a recombinant adeno-associated viral vector (rAAV) in the claimed method.

However, at the time the invention was made, Herzog teaches that AAV viral vectors can be used to deliver therapeutic levels of FIX after intramuscular injection and can be used for treating patients with hemophilia B (page 5804).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson and Bach and Tripathy in further view of Herzog to use rAAV in the claimed methods. One of ordinary skill in the art would have been motivated to use rAAV in the claimed methods because Herzog teaches that AAV viral vectors can be used to deliver therapeutic levels of FIX after intramuscular injection and can be used for treating patients with hemophilia B.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 10/22/03 have been fully considered but they are not persuasive for the same reasons as set forth above in the prior 103(a) rejection.

Response to Arguments

Applicant's arguments, see, filed 10/22/03, with respect to 112 first paragraph rejection have been fully considered and are persuasive. The rejection of claims 1-13, 15, 24, 26, and 28 has been withdrawn because of the amendment to claims 3 and 15. See pages 9 and 10.

Applicant's arguments, see, filed 10/22/03, with respect to 112 second paragraph rejection have been fully considered and are persuasive. The rejection of claims 1 and 13 has been withdrawn because of the amendment to claim 1 and 13. See page 10. However, upon further consideration, a new ground(s) of rejection is made in view of the amendment to claims 17 and 18.

Applicant's arguments, see, filed 10/22/03, with respect to 103(a) have been fully considered and are persuasive. The rejection of claims 13-23, 25, 27, 29 has been withdrawn because of the cancellation of claim 11 and the Statement to Establish Common Ownership of the subject application and US Patent 6,093,392. See page 11.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE - Art Unit 1635, can be reached at (703) 306-3217.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER